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Natriuretic peptides potentiate cardiac hypertrophic response to noradrenaline in rats

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ABSTRACT

Excessive activation of the sympathetic nervous system is involved in cardiovascular damage including cardiac hypertrophy. Natriuretic peptides are assumed to exert protective actions for the heart, alleviating hypertrophy and/or fibrosis of the myocardium. In contrast to this assumption, we show in the present study that both atrial and C-type natriuretic peptides (ANP and CNP) potentiate cardiac hypertrophic response to noradrenaline (NA) in rats. Nine-week-old male Wistar rats were continuously infused with subcutaneous 30 micro-g/h NA without or with persistent intravenous administration of either 1.0 micro-g/h ANP or CNP for 14 days. Blood pressure (BP) was recorded under an unrestrained condition by a radiotelemetry system. Cardiac hypertrophic response to NA was evaluated by heart weight/body weight (HW/BW) ratio and microscopic measurement of myocyte size of the left ventricle. Mean BP levels at the light and dark cycles rose by about 20 mmHg following NA infusion for 14 days, with slight increases in HW/BW ratio and ventricular myocyte size. Infusions of ANP and CNP had no significant effects on mean BP in NA-infused rats, while two natriuretic peptides potentiated cardiac hypertrophic response to NA. Cardiac hypertrophy induced by co-administration of NA and ANP was attenuated by treatment with prazosin or atenolol. In summary, both ANP and CNP potentiated cardiac hypertrophic effect of continuously infused NA in rats, suggesting a possible pro-hypertrophic action of natriuretic peptides on the heart.

1. Introduction

The natriuretic peptide family consists of three bioactive peptides of atrial, B- and C-type natriuretic peptides (ANP, BNP, CNP) [1–3]. A large number of basic and clinical studies have so far been carried out, revealing pivotal roles of natriuretic peptides as circulating or locally-acting hormones in regulating blood pressure (BP) and fluid balance [4–6]. Secreted from the heart, both ANP and BNP were found to lower BP possibly via natriuretic effects in the kidneys and vasodilatation of the resistant vessels [4–6]. CNP is reportedly produced by vascular endothelial cells, acting as a paracrine or autocrine factor protective for damage of the blood vessels [7,8]. Those actions of natriuretic peptides are exerted through two subtypes of specific receptors: A- and B-type natriuretic peptide receptors (NPR-A and NPR-B) [9,10]. NPR-A is relatively specific for ANP and BNP, while NPR-B has an affinity much higher for CNP than for the other two [11]. In comparison with the affinities of NPR-A and B, three NPs bind to the third subtype NPR-C, which functions as a clearance receptor metabolizing the peptides [9,10].

Cardiac hypertrophy is an adaptation of the heart to an augmented preload or afterload, while clinical studies showed that cardiac hypertrophy itself is a risk of future cardiovascular events [12]. Not only the mechanical stress to the heart but also humoral factors, such as angiotensin II or catecholamines, directly stimulate hypertrophy of the myocardium [13,14]. Meanwhile, natriuretic peptides were shown to alleviate hypertrophy and/or fibrosis of the left ventricle and cardiac myocytes by experimental studies with mice lacking the genes of natriuretic peptides or their receptors [15–20], or by those in vitro with cultured cardiac cells [21–23]. Despite those findings, there have been few reports clearly showing that natriuretic peptides exert anti-hypertrophic action independent of BP lowering at physiological doses of the peptides or in patients with hypertension [24]. In the

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meantime, we incidentally found, while doing another series of experiments, that CNP enhanced cardiac hypertrophic response to continuously infused noradrenaline (NA) in rats. Because we have realized a lack of physiological or clinical evidence for anti-hypertrophic action of the peptides, we further verified this unexpected action of natriuretic peptides not only with CNP but also ANP in the present study.

2. Materials and methods

2.1. Animal experiments, peptides, and adrenergic blockers

Animals used in this study were eight-week-old male Wistar rats weighing 292 ± 23 g (mean ± S.D.), which had been purchased from Jackson Laboratory Japan, Yokohama, Japan. L-noradrenaline bitartrate monohydrate (NA) was obtained from Tokyo Chemical Industry Co., Ltd. (Tokyo, Japan), while rat atrial and human C-type natriuretic peptides (ANP-28 and CNP-22) were from Peptide Institute, Inc., Osaka, Japan. Both the alpha1- and beta1-adrenergic blockers, prazosin hydrochloride and atenolol, were purchased from the same company as NA. Rats were maintained under a 12-h light and 12-h dark cycle in a specific pathogen-free condition with standard chow and water given ad libitum during the entire experiment period, including accommodation to new environment, in the Divisions of Bioresources, Frontier Science Research Center, University of Miyazaki. All the surgical procedures were done after confirming the animals thoroughly anesthetized by intraperitoneal injection of 2.0 mg/kg butorphanol tartrate, 1.6 mg/kg midazolam and 0.12 mg/kg medetomidine hydrochloride. The present study was performed in accordance with the Animal Welfare Act and with approval of the University of Miyazaki Institutional Animal Care and Use Committee (No. 2017–509–6).

2.2. Blood pressure and heart rate measurements

Because an important factor for left ventricular hypertrophy is systemic arterial BP level, we evaluated BP changes during the experimental period in conscious, unrestrained rats using a telemetry system (Data Sciences International, St. Paul, MN, USA) with the HD-S10 transmitter implanted in the abdominal cavity. After the accommodation period of 7–10 days, implantation operation was carried out under anesthesia, as previously described [25,26]. In brief, the abdominal cavity was opened by a middle incision and the aorta was isolated from the retroperitoneal tissue. The catheter inserted into the aorta was secured with tissue adhesive and the transmitter was then placed in the intraperitoneal space by suturing to the muscular layer of the abdominal wall. In addition to BP data, we collected locomotive activities from individual animals via this telemetry system as in our previous study [26].

2.3. Administrations of NA, natriuretic peptides, and adrenergic blockers

After the 7-day period of recovery from the implantation operation, rats were divided into eight groups: control, NA, ANP, CNP, NA plus ANP, NA plus CNP, and NA plus ANP groups treated with either prazosin or atenolol. NA dissolved in distilled water containing 0.005% ascorbic acid and 5 mM glutathione was subcutaneously infused into rats at a rate of 30 μg/h via an osmotic mini-pump (Alzet Model 2002; Durect Corp., Cupertino, CA, USA) for 14 days. Both ANP and CNP were co-infused at a rate of 1.0 μg/h with the same model of mini-pump over this experimental period. The continuous infusion of natriuretic peptides was done intravenously to avoid possible enzymatic degradation of the peptides in the subcutaneous tissue, as described previously [27]. The pumps filled with the ANP or CNP peptides dissolved in 0.9% saline were connected to the right jugular vein by a polyethylene catheter (PE-50) and positioned in a pocket constructed in the subcutaneous space. Both prazosin and atenolol were administered via drinking water at doses of 5 and 50 mg/day, respectively, and concentrations of those two drugs were determined by monitoring amounts of water the rats consumed for precise drug administration. The numbers of rats examined were as follows: control, NA, and NA + ANP groups, 8–9; CNP, NA + CNP, and adrenergic blocker-treated groups, 6–7. We carried out 24-h BP monitoring before and after 7 and 14 days of the co-administration period.

2.4. Measurements of myocyte size and collagen volume fraction

After the BP recording at day 14, the animals were sacrificed by drawing the whole blood from the inferior vena cava under anesthesia described above. Then, the heart was immediately excised, weighted, and fixed in 10% formaldehyde. Transverse sections of the cardiac ventricles at the papillary muscle level were stained with hematoxylin-eosin for measurement of myocyte size, or with Sirius red for quantitation of collagen deposition. Both myocyte size and collagen volume fraction of these sections were quantitatively evaluated by a single observer in a blind manner by computerized measurement with a WinROOF2018 software (MITANI Corp., Tokyo, Japan). A total number of 20 myocytes sectioned transversely at the level of nucleus were selected, while omitting oblique-sectioned cells, from four segments of the anterior, lateral, posterior, and septal walls of the left ventricle at a magnification of X200. The selected myocytes were traced and cross-sectional areas of the cells were determined by the software, with resulting mean values being analyzed statistically. To evaluate collagen deposition, the above-mentioned four segments of the Sirius red-stained sections were scanned under polarized light at X40. The obtained images were analyzed, while omitting fibrosis of the perivascular, epi- and endo-cardial areas, and the averages were subjected to the analysis.

2.5. Statistical analysis

All data were analyzed statistically with IBM SPSS software version 28.0 (IBM, Armonk, NY, USA). Multiple comparisons were made with one-way analysis of variance and the Tukey-Kramer method. All data are expressed as the mean ± S.E., otherwise specified, and $P < 0.05$ was considered to be significant.

3. Results

Figs. 1 and 2 show mean BPs and heart rates of the study groups, respectively, at the light and dark cycles before and after 7 and 14 days of the experimental period. Mean BP levels of NA-infused rats were slightly higher than those of controls, but those increases were statistically insignificant except for that at the light cycle of day 14. Neither ANP nor CNP infusions had significant effects on mean BP following NA infusion, while significant reductions were observed in rats co-administered with NA and ANP, which had been treated with prazosin over 14 days (Fig. 1). Fig. 2 is heart rates of the study groups, that were higher during the dark cycle than the light in all groups. Hearts rates remained unchanged following NA infusion with or without co-administration of ANP or CNP at both cycles, except for the NA plus ANP group treated with atenolol. In addition to mean BP and heart rates, we measured locomotive activities of the rats, but no significant differences were noted in those data among the study groups.

Both body weight (BW) and heart weight (HW) of the rats are shown in Table 1, where BW of the atenolol-treated group tended to be lower than that of the other groups, but no significant difference was noted in BW between the NA plus ANP groups treated with or without atenolol. In contrast, clear differences were noted in HW: it significantly increased in both the NA plus ANP and NA plus CNP groups, when compared with the control and NA-infused groups. The effect of NA plus ANP on HW was significantly attenuated by oral treatment with prazosin or atenolol. Fig. 3-A and B are HW/BW ratios and representative photos of hematoxylin-eosin-stained transverse sections of the cardiac ventricles, respectively. Results of HW/BW ratios were identical with those of HW (Table 1): increased HW/BW ratios were seen in the NA plus ANP and

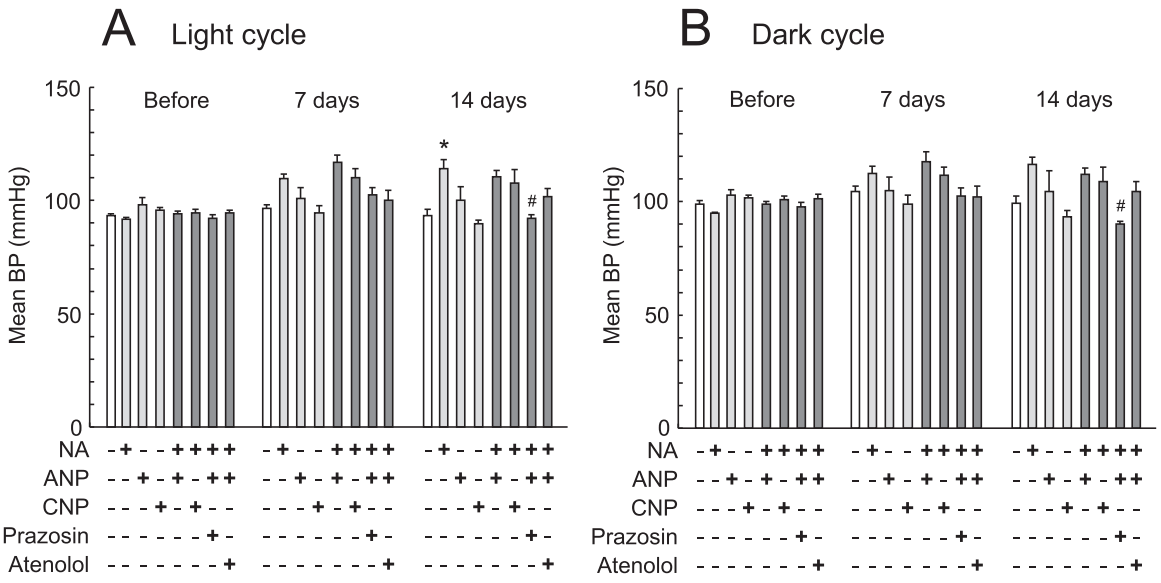

Fig. 1. Mean blood pressure (BP) levels during the light (**A**) and dark (**B**) cycles before and after 7 and 14 days following continuous infusion of noradrenaline (NA). The rats were co-infused with or without (+ or -) atrial or C-type natriuretic peptides (ANP or CNP) and treated with or without (+ or -) prazosin or atenolol. BP levels were measured via an aortic catheter by a telemetry system in conscious, unrestrained rats. Mean ± S.E.; *P < 0.05, vs. control; $^{\#}$P < 0.05, vs NA plus ANP.

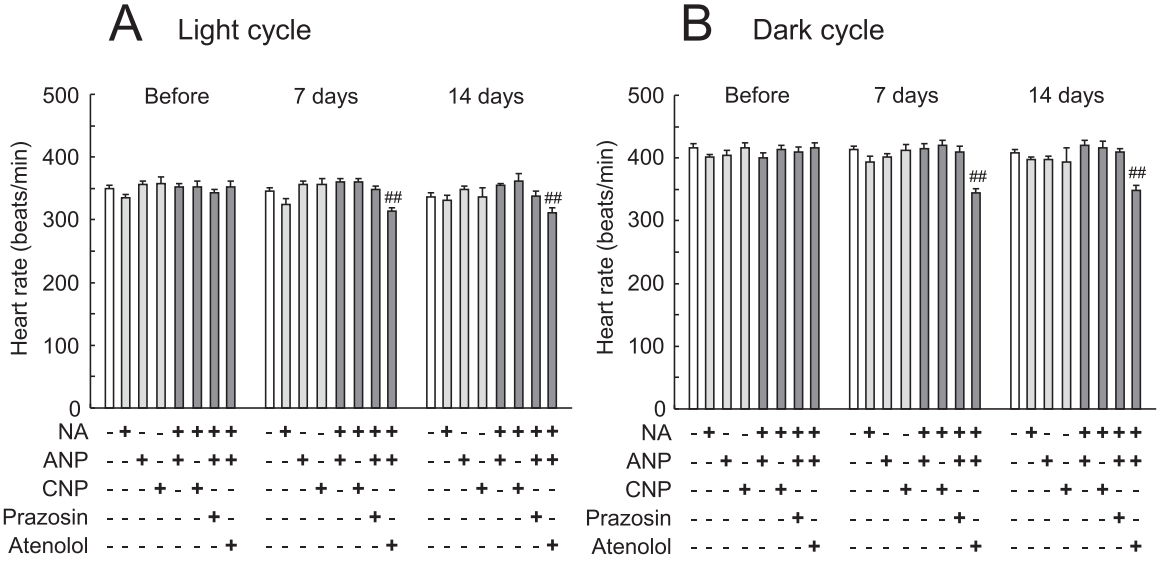

Fig. 2. Heart rates during the light (**A**) and dark (**B**) cycles before and after 7 and 14 days following continuous infusion of noradrenaline (NA). The rats were co-infused with or without (+ or -) atrial or C-type natriuretic peptides (ANP or CNP) and treated with or without (+ or -) prazosin or atenolol. Heart rates were measured via an aortic catheter by a telemetry system in conscious, unrestrained rats. Mean ± S.E.; $^{\#\#}$P < 0.01, vs. NA plus ANP.

Table 1
Body weight and heart weight of the study groups at the end of experiment.

Groups	Body weight (g)	Heart weight (g)
Control	378 ± 5.2	1.05 ± 0.012
Noradrenaline (NA)	380 ± 11.5	1.13 ± 0.003
ANP	347 ± 12.9	0.94 ± 0.034
CNP	367 ± 8.4	1.02 ± 0.024
NA + ANP	347 ± 4.9	1.32 ± 0.050 $^{**+}$
NA + CNP	359 ± 6.8	1.46 ± 0.063 $^{**++}$
NA + ANP + prazosin	373 ± 9.7	1.09 ± 0.047$^{\#\#}$
NA + ANP + atenolol	338 ± 6.0	0.99 ± 0.045$^{\#\#}$

**P < 0.01, vs. Control; $^{+}$P < 0.05, $^{++}$P < 0.01, vs. NA alone; $^{\#\#}$P < 0.01, vs. NA + ANP

NA plus CNP groups, but alleviated by prazosin or atenolol.

In addition to HW and HW/BW ratio, we microscopically examined the left ventricles to see hypertrophy of individual cardiac myocyte and collagen deposition in the ventricular tissues. Fig. 4-A and B show cross-sectional area of myocytes and collagen volume fractions in the left ventricles, respectively. Myocyte size significantly enlarged following co-infusions of NA plus ANP and NA plus CNP, compared to that of the control group. Myocyte enlargement by NA plus ANP was inhibited by treatment with prazosin, while the inhibitory effect of atenolol was statistically marginal. Meanwhile, no significant differences were noted in collagen volume fractions among the study groups.

4. Discussion

In the present study, when infused intravenously, both ANP and CNP

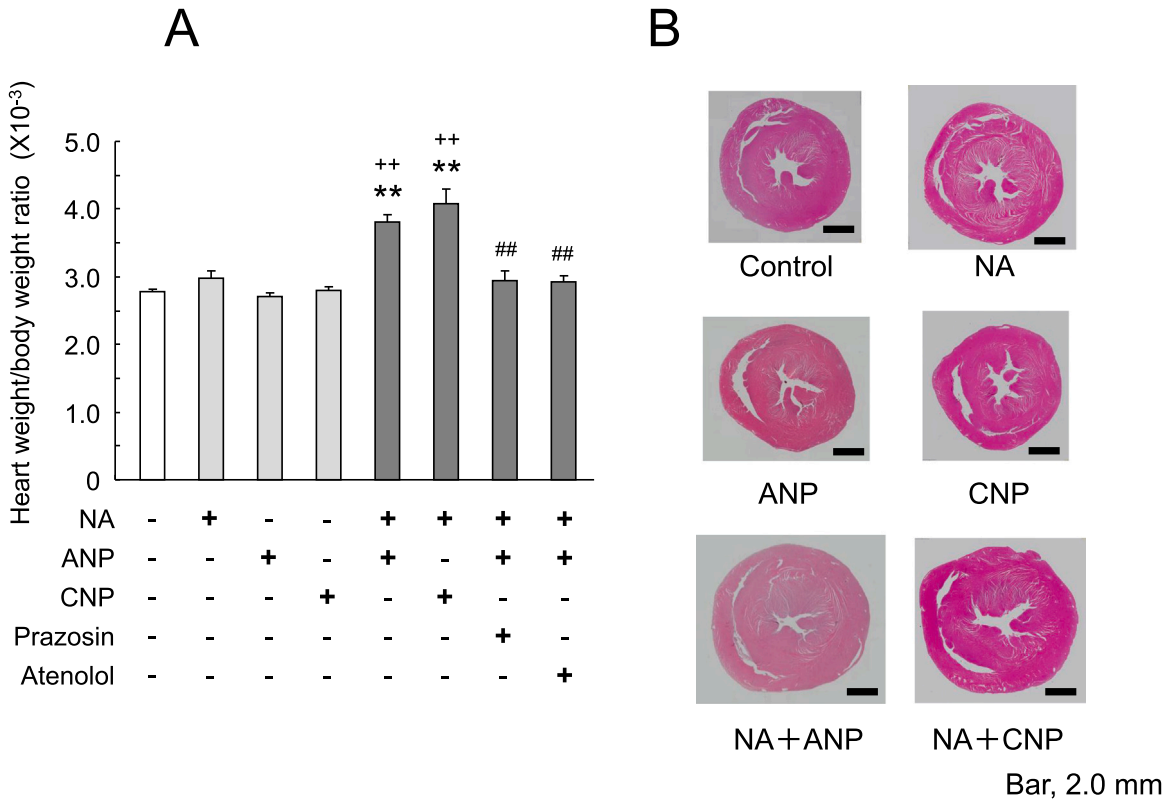

Fig. 3. Heart weight to body weight ratios (**A**) and representative photos of hematoxylin-eosin-stained transverse sections of the cardiac ventricles (**B**). Mean ± S.E.; * *P < 0.01, vs. control; $^{++}$P < 0.01, vs. NA alone; $^{\#\#}$P < 0.01, vs. NA plus ANP; bar, 2 mm.

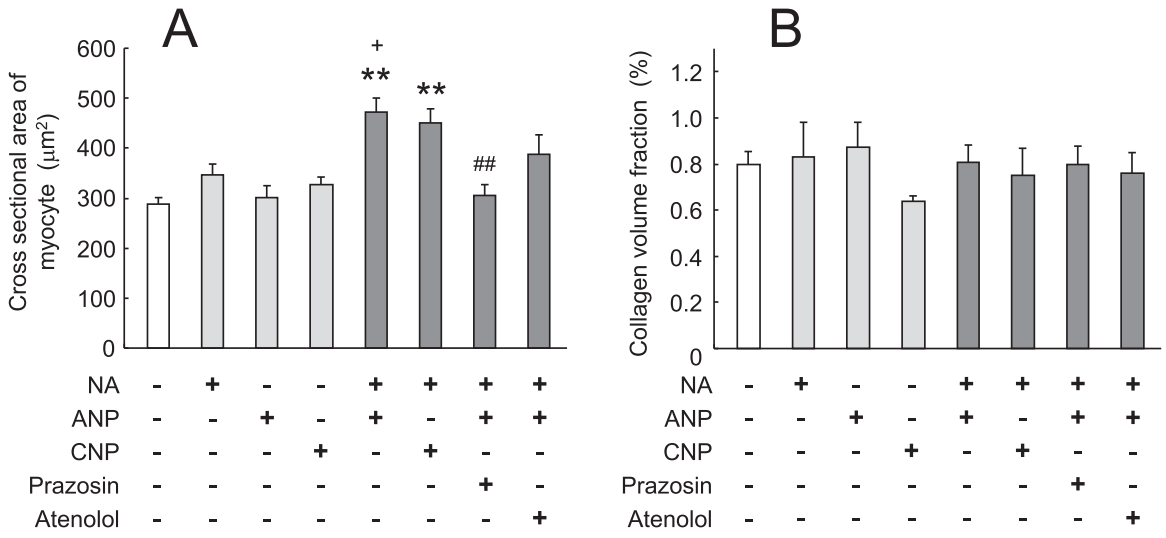

Fig. 4. Cross-sectional area of myocytes (**A**) and collagen volume fractions (**B**) in the left ventricles. Sections of the tissues were stained with hematoxylin-eosin (**A**) or with Sirius red (**B**) and quantitatively evaluated as described under Materials and Methods. Mean ± S.E. * *P < 0.01, vs. control; $^{+}$P < 0.05, vs. NA alone; $^{\#\#}$P < 0.01, vs. NA plus ANP.

were found to enhance cardiac hypertrophic action of NA infused continuously for 14 days. It was only incidentally that we first noticed this unexpected phenomenon while doing another series of experiments. In that experiment, we had been examining whether CNP, a peptide protective for the blood vessels, attenuates 24-h BP variability augmented by continuous infusion of NA [25]. Then we found that ANP similarly potentiated cardiac hypertrophic action of NA and that cardiac hypertrophy induced by co-administration of NA and ANP was alleviated by treatment with either prazosin or atenolol.

Cardiac hypertrophy induced by continuous infusion of NA is assumed to be mediated by two mechanisms: elevation of systemic arterial BP and direct action of NA on ventricular myocytes [14,28]. In this study, mean BP level of the rats infused with NA was slightly higher than that of the controls, but this elevation was modest and mostly, statistically insignificant. Comparable with this, modest increases were observed in HW/BW ratio and size of left ventricular myocytes in NA-infused rats. Meanwhile, co-administration of NA with either ANP or CNP induced significant cardiac hypertrophy without a change in mean

BP levels, suggesting a phenomenon independent of systemic BP.

The natriuretic peptide family, consisting of ANP, BNP, and CNP, was shown to exert the actions protective for the heart and blood vessels presumably via the natriuretic peptide receptors NPR-A and NPR-B [4–6,9,10]. NPR-A mediates the actions of ANP and BNP, while NPR-B has a high affinity for CNP [4–6,11]. Because cardiac hypertrophic response to NA was potentiated similarly by ANP and CNP in the present study, it is possible that both NPR-A and B were involved in the phenomenon observed. In addition to these two receptors, we may raise the possibility that the third subtype of receptor NPR-C, to which three natriuretic peptides bind, also has a role as discussed below [9,10]. It was shown that cardiac hypertrophic action of NA is mediated by both alpha-1 and beta-1 adrenergic receptors [14,28]. In the preset study, potentiation of NA-induced cardiac hypertrophy by ANP was attenuated following treatment with prazosin or atenolol. According to our previous observation [25], neither prazosin nor atenolol had a significant anti-hypertrophic effect in rats infused with NA alone at doses identical to this study. Collectively, both the adrenergic receptors appear to be involved in the potentiation by ANP; meanwhile, it is also possible that BP reductions by prazosin or atenolol may have partly contributed to the attenuated hypertrophic response.

Next, an important point of discussion is the intracellular mechanism via which ANP and CNP potentiated cardiac hypertrophic action of NA infused over 14 days. Activation of the receptors NPR-A and B by ligand binding leads to accumulation of intracellular cGMP, a major second messenger for natriuretic peptides [4–6,9,10]. Qvigstad et al. reported that natriuretic peptides enhanced beta-1 adrenoreceptor signaling of the heart in a cGMP-dependent manner [29]. This enhancement may have resulted in accumulation of cAMP, an intracellular second messenger involved in cardiac hypertrophic action of NA [30]. Meanwhile, according to our unpublished observation, no such potentiation of NA-induced cardiac hypertrophy was detected following treatment with isosorbide mononitrate, which increases intracellular cGMP by activation of soluble guanylate cyclase, suggesting a cGMP-independent mechanism. In this regard, it should be noted that NPR-C, showing an affinity to both ANP and CNP, was reported to have a significant, functional role in the heart [31], and indeed, the two peptides similarly potentiated the effect of NA in this study. In any case, those hypotheses should be verified by future experiments not only with animals in vivo, but also with cultured cardiac cells in vitro.

There have been a number of reports showing the actions of natriuretic peptides, which are protective for the heart and blood vessel. For example, an anti-hypertrophic action of ANP on the myocardium has been found by using mice lacking the genes of ANP or NPR-A and by cultured cardiac cells [15–23]. An important question challenging to us is that our present finding appears contradictory to those reports. Although we currently have no clear explanation for this, we may be able to raise two points for discussion. The first is receptor desensitization following continuous infusion of ANP or CNP, presumably resulting in weakened beneficial actions of the peptides on the heart [32]. Secondly, there have been no reports clearly showing a direct, anti-hypertrophic action of natriuretic peptides on the myocardium, which is exerted at a physiological level of the peptides in a BP lowering-independent manner. In this context, it seems intriguing to note so-called athlete heart, in which physiological hypertrophy occurs following physical exercise [33]. Plasma levels of ANP and BNP were reported to be elevated by exercise in humans [34,35], and in animal studies, not only plasma levels but also gene expressions of the peptides in the cardiac tissues were found to be augmented following physical exercise [36–38].

Recently, LCZ696 (sacubitril/valsartan) has become available for patients with heart failure with reduced ventricular ejection fraction (HFrEF), and in some countries, for those with hypertension [24,39]. This drug lowers BP not only via blocking the angiotensin receptor, but also enhancing the actions of endogenous natriuretic peptides by inhibition of neprilysin which degrades the peptides (4−6). BP-lowering effects of LCZ696 have been reported by a number of clinical trials, while there are few reports showing BP lowering-independent alleviation of cardiac hypertrophy in patients with hypertension [24]. In addition, no significant benefit of LCZ696 was found in a large clinical trial for patients with heart failure with preserved ejection fraction (HFpEF), in which various factors, including myocardial hypertrophy, are assumed to be involved [40]. Thus, it is apparent that the important question raised above needs to be answered by future experiments and/or clinical studies.

5. Conclusions

In the present study, persistent administration of ANP and CNP augmented cardiac hypertrophic response to NA infused continuously for 14 days in rats, suggesting a possible pro-hypertrophic action of natriuretic peptides on the heart.

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CRediT authorship contribution statement

Danfeng Jiang: Investigation, Writing – original draft. **Minami Matsuzaki:** Investigation, Validation. **Takanori Ida:** Writing – review & editing, Investigation. **Kazuo Kitamura:** Writing – review & editing, Methodology. **Toshihiro Tsuruda:** Conceptualization, Methodology. **Koichi Kaikita**: Writing – review & editing, Methodology. **Johji Kato:** Supervision.

Conflict of Interest statement

The authors declare that there are no conflicts of interest.

Data Availability

No data was used for the research described in the article.

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